

WHAT IS CLAIMED IS:

1. An isolated polynucleotide at least 10 bases in length comprising a nucleic acid sequence encoding, or complementary to a nucleic acid sequence encoding, a mammalian receptor for group B  $\beta$ -hemolytic Streptococcus toxin (GBS toxin receptor), or a polypeptide fragment thereof.
- 5 2. The polynucleotide of Claim 1, wherein the polynucleotide is an antisense polynucleotide.
3. The polynucleotide of Claim 1, wherein the nucleic acid sequence comprises SEQ ID NO: 11.
- 10 4. The polynucleotide of Claim 1, wherein the nucleic acid sequence comprises SEQ ID NO: 9.
5. The polynucleotide of Claim 1, wherein the nucleic acid sequence has at least about 87% identity to SEQ ID NO: 1.
6. The polynucleotide of Claim 1, wherein the nucleic acid sequence has 95% identity to the corresponding region of SEQ ID NO: 3 or SEQ ID NO: 7.
- 15 7. The polynucleotide of Claim 1, wherein the nucleic acid sequence has 100% identity to a nucleic acid sequence selected from the group consisting of residues 61 to 1542 of SEQ ID NO: 1, residues 266 to 1870 of SEQ ID NO: 7, and residues 87 to 1568 of SEQ ID NO: 3.
8. The polynucleotide of Claim 1, wherein the polypeptide fragment has an amino acid sequence of the corresponding region of SEQ ID NO: 2, SEQ ID NO: 4 or SEQ ID NO: 8.
- 20 9. The polynucleotide of Claim 8, wherein the polypeptide fragment has the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4 or SEQ ID NO: 8.
10. The polynucleotide of Claim 1, wherein the polynucleotide is hybridizable under high stringency conditions to the nucleic acid sequence of SEQ ID NO: 11.
- 25 11. The polynucleotide of Claim 1, wherein the polynucleotide is hybridizable under high stringency conditions to the nucleic acid sequence of SEQ ID NO: 9.

12. The polynucleotide of Claim 1, wherein the polynucleotide is hybridizable under high stringency conditions to the nucleic acid sequence of SEQ ID NO: 7.

13. The polynucleotide of Claim 1, wherein the polynucleotide comprises a nucleic acid sequence selected from the group consisting of:

- 5 (a) nucleotides 61 to 1542 of SEQ ID NO: 1,
- (b) a DNA sequence encoding the same amino acids as the sequence of (a),
- (c) an RNA sequence corresponding to the sequence of (a), wherein every T is replaced with U,
- 10 (d) an RNA sequence corresponding to the sequence of (b), wherein every T is replaced with U,
- (e) a DNA sequence complementary to the sequence of (a) that specifically hybridizes to the sequence of (a),
- (f) a DNA sequence complementary to the sequence of (b) that specifically hybridizes to the sequence of (b),
- 15 (g) an RNA sequence corresponding to the sequence of (e), wherein every T is replaced with U,
- (h) an RNA sequence corresponding to the sequence of (f), wherein every T is replaced with U,
- 20 (i) nucleotides 87 to 1568 of SEQ ID NO: 3,
- (j) a DNA sequence encoding the same amino acids as the sequence of (i),
- (k) an RNA sequence corresponding to the sequence of (i), wherein every T is replaced with U,
- (l) an RNA sequence corresponding to the sequence of (j), wherein every T is replaced with U,
- 25 (m) a DNA sequence complementary to the sequence of (i) that specifically hybridizes to the sequence of (i),
- (n) a DNA sequence complementary to the sequence of (j) that specifically hybridizes to the sequence of (j),
- 30 (o) an RNA sequence corresponding to the sequence of (m), wherein every T is replaced with U, and
- (p) an RNA sequence corresponding to the sequence of (n), wherein every T is replaced with U.

14. A vector comprising the polynucleotide of Claim 1.
15. A host cell transformed with the vector of Claim 14.
16. The host cell of Claim 15, wherein the polynucleotide is in operative association with a promoter.
- 5 17. The host cell of Claim 15, wherein the GBS toxin receptor or polypeptide fragment is expressed on the cell surface.
18. A process for producing a mammalian GBS toxin receptor or fragment thereof, comprising culturing the host cell of Claim 15 in a suitable culture medium.
- 10 19. An isolated polypeptide comprising a mammalian GBS toxin receptor or fragment thereof.
20. The polypeptide of Claim 19, wherein the fragment is an immunogenic fragment.
21. The polypeptide of Claim 19, wherein the receptor has at least about 86% identity to the corresponding amino acid sequence of SEQ ID NO: 2.
22. The polypeptide of Claim 19, wherein the polypeptide has GBS toxin receptor activity.
- 15 23. The polypeptide of Claim 19, wherein the receptor or fragment has 100% identity to the corresponding region of the amino acid sequence of SEQ ID NO: 4 or SEQ ID NO: 8.
24. The polypeptide of Claim 23, wherein the receptor comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4 and SEQ ID NO: 8.
- 20 25. The polypeptide of Claim 19, wherein the polypeptide is encoded by a nucleic acid sequence hybridizable under high stringency conditions to a nucleic acid sequence selected from the group consisting of:
  - a) nucleotides 61 to 1542 of SEQ ID NO: 1, and
  - b) nucleotides 87 to 1568 of SEQ ID NO: 3.

26. The polypeptide of Claim 19, wherein the GBS toxin receptor is a naturally occurring allelic variant of an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:8.

27. An isolated polypeptide comprising an amino acid sequence that differs from an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4 and SEQ ID NO:8 at no more than about 20% of the amino acid residues.

28. The isolated polypeptide of Claim 27, wherein the amino acid sequence of said isolated polypeptide differs from the amino acid sequence selected from said group at no more than about 1% of the amino acid residues.

29. The isolated polypeptide of Claim 27, wherein the amino acid sequence of said isolated polypeptide differs from the amino acid sequence selected from said group by one amino acid residue.

30. The isolated polypeptide of Claim 27, wherein the different amino acid residues are conservative substitutions of the corresponding residues of the amino acid sequence selected from said group.

31. An isolated polypeptide comprising an amino acid sequence of the formula:

AA1-AA<sub>n</sub>-AA<sub>m</sub>

wherein:

AA1 is absent or is M;

AA<sub>n</sub> is a contiguous chain of 0 to 100 amino acids, preferably of 0 or 41 amino acids, even more preferably of residues 2-42 of SEQ ID NO:8; and

AA<sub>m</sub> is a contiguous chain of 494 amino acids comprising AA43 through AA536, wherein:

(1) each of AA43, AA47, AA51, AA52, AA57, AA58, AA65, AA66, AA72, AA85, AA87, AA93, AA94, AA96, AA115, AA116, AA122, AA123, AA125, AA134, AA143, AA173, AA174, AA178, AA185, AA186, AA189, AA190, AA196, AA200, AA204, AA206, AA207, AA220, AA253, AA260, AA276, AA277, AA280, AA283, AA287, AA294, AA295, AA298, AA300, AA301, AA312, AA324, AA326, AA360, AA365, AA373, AA374, AA379, AA396, AA403, AA407, AA418, AA480, AA483, AA486, AA491, AA494, AA502, AA528, AA529, AA532 and AA536 is an amino acid residue corresponding to:

(a) residue 43, 47, 51, 52, 57, 58, 65, 66, 72, 85, 87, 93, 94, 96, 115, 116, 122, 123, 125, 134, 143, 173, 174, 178, 185, 186, 189, 190, 196, 200, 204, 206, 207, 220, 253, 260, 276, 277, 280, 283, 287, 294, 295, 298, 300, 301, 312, 324, 326, 360, 365, 373, 374, 379, 396, 403, 407, 418, 480, 483, 486, 491, 494, 502, 528, 529, 532 and 536, respectively, of SEQ ID NO:8;

(b) residue 2, 6, 10, 11, 16, 17, 24, 25, 31, 44, 46, 52, 53, 55, 74, 75, 81, 82, 84, 93, 102, 132, 133, 137, 144, 145, 148, 149, 155, 159, 163, 165, 166, 179, 212, 219, 235, 236, 239, 242, 246, 253, 254, 257, 259, 260, 271, 283, 285, 319, 324, 332, 333, 338, 355, 362, 366, 377, 439, 442, 445, 450, 453, 461, 487, 488, 491 and 495, respectively of SEQ ID NO:4; or

(c) a conservative substitution thereof;

(2) each of AA44-AA46, AA48-AA50, AA53-AA56, AA59-AA64, AA67-AA71, AA73-AA84, AA86, AA88-AA92, AA95, AA97-AA114, AA117-AA121, AA124, AA126-AA133, AA135-AA142, AA144-AA172, AA175-AA177, AA179-AA184, AA187-AA188, AA191-AA195, AA197-AA199, AA201-AA203, AA205, AA208-AA219, AA221-AA252, AA254-AA259, AA261-AA275, AA278-AA279, AA281-AA282, AA284-AA286, AA288-AA293, AA296-AA297, AA299, AA302-AA311, AA313-AA323, AA325, AA327-AA359, AA361-AA364, AA366-AA372, AA375-AA378, AA380-AA395, AA397-AA402, AA404-AA406, AA408-AA417, AA419-AA478, AA481-AA482, AA484-AA485, AA487-AA490, AA492-AA493, AA495-AA501, AA503-AA527, AA530-AA531 and AA533-AA535 is

(a) residue 44-46, 48-50, 53-56, 59-64, 67-71, 73-84, 86, 88-92, 95, 97-114, 117-121, 124, 126-133, 135-142, 144-172, 175-177, 179-184, 187-188, 191-195, 197-199, 201-203, 205, 208-219, 221-252, 254-259, 261-275, 278-279, 281-282, 284-286, 288-293, 296-297, 299, 302-311, 313-323, 325, 327-359, 361-364, 366-372, 375-378, 380-395, 397-402, 404-406, 408-417, 419-478, 481-482, 484-485, 487-490, 492-493, 495-501, 503-527, 530-531 and 533-535, respectively, of SEQ ID NO:8; or

(b) a conservative substitutions thereof; and

(3) one or more of AA315 through AA367 are optionally absent.

32. The isolated polypeptide of Claim 31, wherein the polypeptide is a hybrid polypeptide comprising less than all the amino acid residues of SEQ ID NO:2 that are different from the corresponding amino acid residues of SEQ ID NO:8 and less than all the amino acid residues of SEQ ID NO:8 that are different from the corresponding amino acid residues of SEQ ID NO:2.

33. An antibody that recognizes a mammalian GBS toxin receptor or fragment thereof.

34. The antibody of Claim 33, wherein the receptor or fragment comprises amino acid residues 7 to 22 of SEQ ID NO:4.

35. The antibody of Claim 33, wherein the receptor or fragment comprises amino acid residues 71 to 84 of SEQ ID NO:4.

36. The antibody of Claim 35, wherein the receptor is expressed on the surface of a cell.

37. An isolated complex comprising a GBS toxin bound to a mammalian GBS toxin receptor or fragment thereof.

38. A method of forming a complex comprising:

contacting a GBS toxin with a polypeptide comprising a mammalian GBS toxin receptor, or fragment thereof that can bind GBS toxin, under conditions that permit specific binding of the GBS toxin to the polypeptide, and

allowing the complex to form.

39. A method for purifying a compound that binds a GBS toxin receptor, which method comprises:

5 providing a polypeptide comprising a mammalian GBS toxin receptor or fragment thereof that binds GBS toxin;

contacting said polypeptide with a sample comprising the compound under conditions that allow specific binding of the compound to the polypeptide; and

separating the bound compound from the remainder of the sample.

10 40. A method of determining the presence or absence of GBS toxin in a sample, which method comprises:

contacting the sample with a polypeptide comprising a mammalian GBS toxin receptor, or fragment thereof that can bind GBS toxin, under conditions that permit specific binding of the GBS toxin to the polypeptide,

and determining whether specific binding has occurred.

15 41. A method for diagnosing early onset disease in a neonate comprising performing the method of Claim 40, wherein the sample is obtained from the neonate and wherein presence of the GBS toxin is indicative of early onset disease.

42. A method for detecting pathologic vasculature in a mammalian tissue, which method comprises detecting the presence of a GBS toxin receptor.

20 43. The method of Claim 42, wherein the detecting comprises using an antibody that specifically recognizes the GBS toxin receptor.

44. The method of Claim 42, wherein the presence of GBS toxin receptor is indicative of metastasis of a cancerous tumor.

25 45. A method for identifying a compound which inhibits binding of a GBS toxin to a mammalian GBS toxin receptor, comprising:

combining a test compound with a polypeptide comprising a mammalian GBS toxin receptor, or fragment thereof that can bind GBS toxin, in a reaction mixture containing GBS toxin and

under conditions that permit specific binding of the GBS toxin to the receptor or fragment, and  
determining the amount of inhibition by the compound of the binding of the GBS toxin to  
the polypeptide.

46. An inhibitor of binding of a GBS toxin to a mammalian GBS toxin receptor.

5 47. A method for identifying a compound which specifically binds a mammalian GBS toxin  
receptor, comprising:

combining a test compound with a polypeptide comprising a mammalian GBS toxin  
receptor or fragment thereof that can bind GBS toxin, under conditions that allow specific binding to  
occur, and

10 detecting a complex formed between said test compound and said polypeptide.

48. The method of Claim 47, further comprising combining said GBS toxin with said  
polypeptide in the presence and absence of said test compound and comparing said specific binding of  
GBS toxin to said polypeptide in the presence or absence of said test compound, wherein decreased  
specific binding of GBS toxin in the presence of said test compound relative to the specific binding of  
15 GBS toxin in the absence of said test compound is indicative of the ability of said test compound to bind  
said mammalian GBS toxin receptor.

49. A method for determining cytotoxicity of a test chimeric compound, which method  
comprises:

20 exposing a cell expressing, on the cell surface, a mammalian GBS toxin receptor, or  
fragment thereof that binds GBS toxin, to a test chimeric compound comprising a cytotoxic agent  
coupled to said GBS toxin; and  
detecting signs of cytotoxicity.

50. A chimeric compound comprising a cytotoxic agent covalently linked to a molecule that  
specifically binds a mammalian GBS toxin receptor.

25 51. A method for identifying an inhibitor of GBS toxin receptor, which method comprises:

incubating test cells in the presence and absence of a test compound and under conditions  
in which the cells incubated in the absence of the test compound can proliferate or migrate, wherein the  
test cells express GBS toxin receptor or a fragment thereof having GBS toxin receptor activity; and

comparing the proliferation or migration of the test cells incubated in the presence of the test compound to the proliferation or migration of the test cells incubated in the absence of the test compound, wherein less proliferation or migration in the presence of the test compound is indicative of the test compound being an inhibitor of the GBS toxin receptor.

5           52.     The method of Claim 51, which method further comprises:

incubating the control cells in the presence and absence of the test compound, comparing the proliferation or migration of the test cells to the control cells; and

10           comparing the proliferation or migration of the control cells incubated in the presence of the test compound to the proliferation or migration of the control cells incubated in the absence of the test compound, wherein, in the absence of a difference in proliferation or migration of the control cells incubated in the presence or absence of the test compound, less proliferation or migration in the presence of the test compound is indicative of the test compound being a specific inhibitor of the GBS toxin receptor.

15           53.     A method for identifying an inhibitor of endothelial cell proliferation or migration, which method comprises:

incubating test endothelial cells in the presence and absence of a test compound and under conditions in which the cells incubated in the absence of the test compound can proliferate or migrate, wherein the test cells express GBS toxin receptor or a fragment thereof having GBS toxin receptor activity; and

20           comparing the proliferation or migration of the test cells incubated in the presence of the test compound to the proliferation or migration of the test cells incubated in the absence of the test compound, wherein less proliferation or migration in the presence of the test compound is indicative of the test compound being an inhibitor of the endothelial cell proliferation or migration.

25           54.     A method for identifying a therapeutic compound for the treatment or prevention of a medical condition characterized by pathologic angiogenesis or neovascularization, which method comprises:

incubating test cells in the presence and absence of a test compound, wherein the test cells express GBS toxin receptor or a fragment thereof having GBS toxin receptor activity;

30           comparing the proliferation or migration of the test cells incubated in the presence of the test compound to the proliferation or migration of the test cells incubated in the absence of the test



compound, wherein less proliferation or migration in the presence of the test compound is indicative of the test compound being a candidate therapeutic compound for the treatment or prevention of the medical condition.

55. The method of Claim 54, wherein the medical condition is a cancerous tumor.

5 56. The method of Claim 54, wherein the medical condition is a reperfusion injury.

57. The method of Claim 54, wherein the medical condition is scarring during wound healing.

58. The method of Claim 54, wherein the medical condition is keloids.

10 59. The method of Claim 54, wherein the medical condition is a chronic inflammatory disease.

60. The method of Claim 54, wherein the medical condition is neural injury.

61. A method for identifying a compound which inhibits binding of a GBS toxin to a mammalian GBS toxin receptor, comprising:

- 15
- (a) simulating and selecting the most probable conformations of a mammalian GBS toxin receptor,
  - (b) designing a chemically modified analog that substantially mimics the energetically most probable three-dimensional structure of the polypeptide,
  - (c) chemically synthesizing the analog, and
  - (d) evaluating the bioactivity of the analog.

20 62. The method of 61, wherein steps (a) and (b) are performed with the aid of a computer program.

63. A method for identifying a compound which binds to a mammalian GBS toxin receptor, comprising:

- 25
- (a) simulating and selecting the most probable conformations of a mammalian GBS toxin receptor,
  - (b) deducing the most probable binding domains of the polypeptide,

- (c) designing a compound that would form the energetically most probable complexes with the polypeptide,
- (d) chemically synthesizing the compound, and
- (e) evaluating the bioactivity of the compound.

5            64.    The method of 63, wherein steps (a)-(c) are performed with the aid of a computer program.

65.    A method for the prevention or treatment of neonatal onset disease in a human neonate, comprising administering an inhibitor of binding of GBS toxin to a human GBS toxin receptor.

10           66.    The method of Claim 65, wherein the inhibitor is a GBS toxin receptor neutralizing antibody.

67.    A method for inhibiting pathologic or hypoxia-driven endothelial cell proliferation or migration in a mammalian tissue, which method comprises specifically binding a molecule to a GBS toxin receptor present on the surface of at least one cell in the tissue, the molecule being selected from the group consisting of:

15                    a compound that can evoke an inflammatory response when bound to a GBS toxin receptor in a mammal;

                    a chimeric compound comprising a cytotoxic compound coupled to a compound that specifically binds the GBS toxin receptor;

20                    an inhibitor of GBS toxin receptor phosphorylation; and  
                    an inhibitor of GBS toxin receptor activity.

68.    The method of Claim 67, wherein a pharmaceutically effective amount of the molecule is administered to a mammal comprising the mammalian tissue.

69.    The method of Claim 68, wherein the mammal has a cancerous tumor.

70.    The method of Claim 68, wherein the mammal has a chronic inflammatory disease.

25           71.    The method of Claim 68, wherein the mammal has a wound.

72.    The method of Claim 68, wherein the mammal has keloids.

73. The method of Claim 68, wherein the mammal has a neural injury.
74. The method of Claim 68, wherein the mammal has a reperfusion injury.
75. The method of Claim 67, wherein the inhibitor is a kinase inhibitor.
76. The method of Claim 67, wherein the inhibitor is a single chain antibody specific for the
- 5 GBS toxin receptor.
77. The method of Claim 67, wherein the inhibitor is an antisense polynucleotide that specifically hybridizes under high stringency conditions to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3 and SEQ ID NO:7.
78. A pharmaceutical composition comprising a pharmaceutically effective amount of an
- 10 inhibitor of a GBS toxin receptor, and a pharmaceutically acceptable carrier.
79. A pharmaceutical composition comprising a pharmaceutically effective amount of a chimeric compound comprising a cytotoxic agent coupled to a compound that binds GBS toxin receptor, and a pharmaceutically acceptable carrier.
80. A kit comprising a GBS toxin receptor or fragment.
81. A kit comprising a reagent for detecting the presence of a GBS toxin receptor or fragment
- 15 or of a polynucleotide encoding the GBS toxin receptor or fragment.